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rdenison@environmentaldefense.org

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To: NCIC OPPT@EPA, ChemRTK HPV@EPA, Rtk Chem@EPA, NCIC HPV@EPA, Karen Boswell/DC/USEPA/US@EPA, Tadams@therobertsgroup.net
cc: MTC@mchsi.com, kflorini@environmentaldefense.org, rdenison@environmentaldefense.org
Subject: Environmental Defense comments on Ketone Bottoms (CAS# 68990-20-5)

(Submitted via Internet 6/29/04 to oppt.ncic@epa.gov, hpv.chemrtk@epa.gov, boswell.karen@epa.gov, chem.rtk@epa.gov, MTC@mchsi.com, and Tadams@therobertsgroup.net)

Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for Ketone Bottoms (CAS# 68990-20-5).

The Eastman Chemical Company, in response to EPA's High Production Volume (HPV) Chemical Challenge, has submitted robust summaries and a test plan describing available data to address SIDS elements required for the chemical mixture known as Ketone Bottoms 4 (KB4). According to this submission "... Ketone Bottoms 4 (KB4) consists of a continually varying mixture of linear- and branched-chain aliphatic ketones possessing carbon chain lengths from C9 to C12." KB4 is said to contain some of the same chemicals as Ketone Bottoms 3 (KB3), which consists of a mixture of linear- and branched-chain aliphatic ketones possessing carbon chain lengths from 9 to 15 carbons. KB3 consists primarily of isomers of undecanone (35%), cyclohexanone (11%) and pentadecanone derivatives (5%).

This submission appears to address both KB4 and KB3, but that is not clearly stated. We also note that Page 5 of the test plan indicates the content of ketone bottoms is not well-defined. Ketones apparently account for approximately 50% of KB4. Other constituents of KB4 include dimethylcyclohexanones (10.8%) and 6-methyl-2-heptanone (2.5%). However, the remaining approximately 37% of the KB4 appears to be comprised of unidentified chemicals. Likewise, it appears that only about 50% of the composition of KB3 is comprised of identified chemicals. The remaining matter is "assumed" by the sponsor to be of similar molecular weight and structure. It would not seem that a discussion of a chemical mixture could be considered complete if it does not address a very large percentage of the total chemicals in that mixture.

Many of the ketones in this mixture have both synthetic and natural origins and are found in fruits, cheeses, meats and some vegetables. According to this submission, the FDA has recognized some of the ketones in this category as safe for human consumption. Also, the Joint Expert Committee of the World Health Organization has reviewed a number of these ketones and approved their use as flavorings at current levels of intake in the diet. Based on this information, this submission infers that most ketones in this mixture present a minimal threat to the environment or human health when encountered at low levels.

We appreciate that minimal background information is required in submissions such as this one. However, it would be appreciated if the test plan could provide information regarding the production, transport and use of these ketone bottoms and descriptions of potential sources of release that could result in environmental and/or human exposure.

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The test plan does provide a thorough discussion of the metabolism of individual constituents of this mixture. Metabolism of aliphatic ketones occurs primarily via reduction to the corresponding secondary alcohol, conjugation with glucuronic acid and excretion in urine. Alkyl-substituted cyclohexanones are interconvertible with their corresponding alcohols that are conjugated with glucuronic acid and excreted primarily in urine. However, it is pointed out briefly in the test plan that some ketones may be metabolized to neurotoxic chemicals. These ketones undergo omega- and/or omega-1 oxidation to form gamma-diketones (e.g. 2,5-hexanedione) that induce neurotoxicity associated with "giant axonal swelling". Little more is said about this phenomenon. The considerable research on this phase of ketone metabolism has been largely ignored in this submission. For example, a brief search for studies of one such ketone, 2,5-hexanedione, turned up over 700 references. This aspect of ketone toxicity should be discussed in greater detail.

The extensive test plan and robust summaries submitted for ketone bottoms describe a great deal of data for some individual constituents of the mixture. However, Environmental and Human Toxicity are not addressed for the large majority of the individual chemicals. Many of those chemicals not addressed do have many structural similarities to those that are addressed; we defer to EPA as to whether the data that are available for a few chemicals in this mixture are sufficient to represent the entire mixture. However, we are concerned that it appears no studies have been conducted directly on the mixtures of chemicals that constitute KB4 and KB3, the actual subject of this submission.

Data that are available indicate those chemicals in this mixture that have been studied exhibit considerable aquatic toxicity. Fortunately, they do not seem to persist in the environment and they appear to have relatively little toxicity to mammals when administered acutely or in repeat dose studies. Genotoxicity data are available for a few chemicals, which indicate they are not mutagenic when tested in the Ames system or in chromosomal aberration assays. A host-mediated assay was positive for one chemical when administered at a very high dose, but that is most probably not relevant. Chronic studies of 3,5,5-trimethylcyclohexenone were positive for renal effects in male rats; however, other work has demonstrated that the mechanism involved, accumulation of alpha-2-microglobulin, is not relevant to humans and does not occur in female rats or in either sex of mice.

At over 200 pages, the robust summaries appear extensive, but they in fact contain few data for most of the chemicals in this mixture. Data are available for some representatives of the group, whereas others are addressed by one or a few studies and most chemicals in this category have apparently not been studied at all.

The weakest data in this submission appear to be those descriptions of studies of reproductive/developmental toxicity. A few of these studies are recent, carefully designed and conducted under GLP, and indicate the ketones tested have no apparent reproductive/developmental toxicity when administered at doses that are not toxic to the dams. However, review of most of the studies described in the robust summaries indicates they are of poor quality. Many of these studies are somewhat dated and were not

conducted under GLP. In many cases they fail to describe the purity of test compound or used impure test compounds. In still other cases, the test compound is given as one chemical whereas the test was apparently conducted using another chemical. Admittedly the second chemical is identified in each case and is always closely structurally related to the first, but it is not clear why the chemical tested is not described as the test chemical. A number of studies used only one dose.

In summary, each section of the test plan concludes with a statement that "no further testing is required" or something to that effect. We do not agree. We recommend against accepting this proposal because available and acceptable data address the SIDS elements for only a few constituents of the ketone bottoms mixture. No data have been generated using the mixture directly as the test substance. Further, most available data for reproductive/developmental toxicity are generally inadequate. Whereas we appreciate that ketone bottoms are varying mixtures that will be difficult to characterize, we think current data are insufficient to address this complex mixture. Greater than 30% of the composition of KB4, and approximately 50% of the composition of KB3 are unidentified. Data for individual chemicals cannot be bridged to predict the toxicity of unknown chemicals even if they are "thought" to be related. At present there are no studies to ascertain the possibility of synergism or the effect of the considerable impurities present in these mixtures. Therefore, we recommend that studies using representative samples of KB4 and KB3 be designed and conducted according to OECD guidelines to address each of the SIDS elements required for environmental and human toxicity.

Thank you for this opportunity to comment.

Hazel B. Matthews, Ph.D.
Consulting Toxicologist, Environmental Defense

Richard Denison, Ph.D.
Senior Scientist, Environmental Defense